Drug-Induced Lupus, a One-time Hit or a Harbinger of Future Autoimmunity: A Case Report

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ABSTRACT

Introduction: Drug-induced lupus (DIL) can comprise up to 10% of new lupus cases annually, and the list of medications associated with DIL is increasing. However, it can be difficult to recognize the connection between symptoms and a medication-induced autoimmune syndrome, which can lead to an invasive, costly workup. Given that the prognosis is usually good if therapy with the offending agent is stopped, it is important to identify this clinical entity promptly.

Case Presentation: A healthy, 44-year-old man with hypertension was seen initially because of shoulder pain and again after development of fevers and chest pain. He underwent a thorough infectious workup and then oncologic workup, with his clinical course complicated by a *Histoplasma* infection. After evaluation by subspecialists, the patient was thought to have an autoimmune condition related to DIL. His symptoms improved after he discontinued the offending drug therapy and received a course of corticosteroids.

Discussion: Our case highlights how DIL should be on the differential when seemingly disparate symptoms develop in a patient receiving DIL-associated medications. Lupus is one of the "great imitators," in which symptoms can be ascribed to many different underlying causes. Although this patient's presentation may have been confounded by concomitant histoplasmosis, his improvement with cessation of hydralazine treatment argues in favor of DIL. His continued atypical serologic test results could be residual from his DIL and should normalize with time. However, it raises the question whether this bout of DIL has unmasked a previously quiescent autoimmune condition, requiring continued observation.

INTRODUCTION

Drug-induced lupus (DIL) is a condition that many physicians learn about during medical school then tend to forget. Nevertheless, several studies indicate that DIL can comprise up to 10% of new lupus cases every year, and the list of medications associated with DIL is increasing.[1-3] However, even when the level of suspicion for DIL is relatively high, it can be difficult to recognize the connection between symptoms and a medication-induced autoimmune syndrome. Without proper recognition of its symptoms, DIL may lead to an extensive, costly workup. Given that the prognosis is usually good if therapy with the offending agent is stopped, it is important to identify this clinical entity as soon as possible. We present a case of DIL diagnosed after an extensive workup.

CASE PRESENTATION

Presenting Concerns

A 44-year-old man presented to his primary care physician on July 11, 2018, for evaluation of acute-onset, right shoulder pain without any preceding trauma. The patient was vegetarian, regularly did aerobic exercise, and had no history of smoking or alcohol use. His medical history was notable only for hypertension, for which he received hydrochlorothiazide, hydralazine, and losartan. His shoulder pain was thought to be benign.

Therapeutic Intervention and Treatment

Initially, the patient underwent a course of nonsteroidal anti-inflammatory drugs and physical therapy. His pain subsequently resolved.

Follow-up and Outcomes

Three weeks after the right shoulder pain resolved, new intermittent pain developed in the left shoulder. Because of the severity of the pain, he had decreased range of motion and was waking up during the night. He denied any frank swelling or warmth of the joints but had noted periodic pain in the wrists (right more than left) and in his hand (distal interphalangeal joints) with range of motion. He was seen by his primary care physician and then by an orthopedic physician, who thought the hands and wrists were fine but that he may have had bilateral rotator cuff syndrome. He was offered a magnetic resonance image to evaluate for a partial tendon tear as well as a corticosteroid injection into the subacromial space, but he declined both at the time.

Given multiple joint involvement, including his hands and wrists, serologic laboratory tests were performed. The results included a normal rheumatoid factor, negative anticyclic citrullinated peptide antibody (anti-CCP), and a slightly elevated erythrocyte sedimentation rate to 39 mm/h. Bilateral shoulder impingement syndrome was diagnosed, and conservative treatment with nonsteroidal anti-inflammatory drugs, shoulder exercises, activity modification, and physical therapy was recommended. However, given the elevated erythrocyte sedimentation rate, there was a suggestion of inflammatory arthritis. A 15-day

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course of 15 mg of prednisone daily was empirically trialed, with complete resolution of the joint and muscle pain.

Shortly after having completed his corticosteroid course, the patient started experiencing periodic fevers, chest pain, and cough. An upper respiratory tract infection was diagnosed. However, because of persistent symptoms, he visited the Emergency Department. At that point, a full battery of laboratory tests was performed, and results demonstrated normal C3/C4 levels, normal aldolase level, normal rheumatoid factor, negative anti-CCP, and positive antinuclear antibodies (ANA), particularly antidouble-stranded (ds) DNA (17 IU/mL) and anti-Scl-70 (1.1 antibody index). Concurrently, procalcitonin and lactate levels were elevated to 0.17 ng/mL and 3.5 mmol/L, respectively. It was thought that he had a postviral cough, but a computed tomography (CT) scan of the chest showed esophagitis and mediastinitis. This was thought to be secondary to excessive coughing. He had a fluoroscopic esophagram, for which the results were normal. No esophagogastroduodenoscopy was done at that time, but results of an infectious disease workup were notable for a positive urine *Histoplasma* antigen. Therefore, the patient was given a trial of itraconazole therapy. He continued to have some intermittent symptoms.

A month later he also tested positive for *Coxiella* immunoglobulin M antibody, but it was unclear whether this was clinically significant. A repeated chest CT scan 1 month after the first CT showed improvement in esophagitis and mediastinitis but demonstrated small bilateral pleural effusions with normal complement levels. Additionally, a maculopapular rash developed, particularly pronounced over the dorsal aspects of the feet. It was thought to be a drug-related rash, so the patient's regimen of hydrochlorothiazide, which he took for blood pressure control, was discontinued.

Because of the patient's persistent lymphadenopathy and other systemic symptoms, an oncologic workup was also undertaken. A peripheral blood test result showed microcytic anemia. A bone marrow biopsy and positron emission tomography scan were performed. The scan showed mildly hypermetabolic subcentimeter nodes above and below the level of the diaphragm, which the radiologist thought could be reactive. This finding was thought to be supportive of the clinical diagnosis of granulomatous infection and less likely a possible lymphoproliferative process. His flow cytometry results and bone marrow biopsy specimen were both normal.

On looking at the overall presentation along with the patient's medication list, there was concern that the symptoms could be related to DIL. An antihistone antibody was checked on October 25, 2018, and came back positive. At this point, 3.5 months after his initial presentation, the patient was presumed to have either DIL related to hydralazine use or native systemic lupus erythematosus (SLE). His hydralazine treatment was stopped, and he was started on a course of prednisone and hydroxychloroquine. His symptoms resolved. His antihypertensive medications were also switched to clonidine and chlorthalidone.

The patient had a follow-up 3 months later in the rheumatology clinic and was still feeling well. Interestingly, on March 29, 2019, the patient tested positive for lupus anticoagulant. Although the level of his antihistone antibody was lower than before, it was still positive, as were anti-dsDNA and anti-Scl 70 antibodies. Continued follow-up with a rheumatologist is planned. The patient gave informed consent to allow publication of his case. Table 1 provides a timeline of the case.

DISCUSSION

SLE is one of the most common autoimmune diseases. It occurs in 15,000 to 30,000 cases per year, of which approximately 10% can be related to drugs.[1,3] According to Xiao et al[1], DIL "is the most common form of an iatrogenic autoimmune disease." Hydralazine is an antihypertensive medication that has been associated with DIL as well as antineutrophil cytoplasmic antibody vasculitis.[4] Iyer and colleagues[5] state: "Hydralazine-induced lupus syndrome was first reported in 1953. The syndrome occurs in 5–10% of patients taking hydralazine, and clinical manifestations include arthralgia, myalgia, fever, and serositis." Musculoskeletal symptoms are the most common clinical manifestations. It rarely manifests as pericardial effusion, cardiac tamponade, pleural effusion, or pulmonary edema. Iyer et al additionally note[5]:

After the publication of the African-American Heart Failure trial [in 2004], there was a significant increase in the amount of hydralazine prescribed to patients with heart failure. … Risk factors that have been linked to hydralazine–induced lupus include high daily doses (> 200 mg/d), slow acetylator status, HLA-DRw4 phenotypes, therapy longer than 3 months, female sex, and a family history of autoimmune disease.

In about 95% of patients with DIL, the serum is positive for ANA; however, ANA-negative DIL, although rare, has been described.[5]

Both DIL and SLE are ANA positive. Although antihistone antibodies are classically associated with DIL, they have poor specificity because they can occur in up to 50% of patients with SLE as well as in other rheumatic diseases such as scleroderma or rheumatoid arthritis.[2,6] Surprisingly, not all forms of DIL are created equal, as antihistone antibodies have been detected in 32%, 42%, and less than 50% of DIL associated with minocycline, propylthiouracil, and statins, respectively.[2] According to Araújo-Fernández et al[2]:

The presence of anti–Smith antibodies is almost exclusively found in idiopathic SLE [but is rarely found in DIL]. … Antiphospholipid antibodies and lupus anticoagulant have been described in some cases of DIL. … Curiously, serologic abnormalities, especially antihistone antibodies, may persist much longer than the symptoms of DIL, which resolve over days or weeks after drug discontinuation.

There are multiple theories as to how hydralazine induces DIL. Per Kumar et al[4]:

[it] is known that hydralazine tends to accumulate in the intracytoplasmic neutrophilic granules. This accumulation leads to binding to myeloperoxidase, which leads to release of cytotoxic products and cell death. Once the neutrophils have undergone cell death, antigens that are normally sequestered are exposed, enabling uptake by antigen-presenting cells and production of antineutrophil cytoplasmic antibodies.

Other hypotheses that have been proposed regarding how hydralazine can cause an autoimmune response include "increased expression of neutrophil autoantigens through the reversal of

Table 1. Timeline of the case

Date	Summaries from initial and follow-up visits	Diagnostic testing	Interventions
7/11/18	Patient saw PCP because of right shoulder joint pain for past wk	Physical examination	Diagnosed with shoulder impingement syndrome; pain resolved with PT
7/23/18	Patient had left hand and left shoulder pain	Hand radiographs, serum ESR, RF, and anti-CCP	Diagnosed with de Quervain tenosynovitis of left hand. Advised to continue PT and take naproxen
7/24/18	ESR elevated at 39 mm/h, thought to be caused by inflammatory reaction to shoulder impingement. Normal RF and anti-CCP levels. Results of hand radiographs were normal	Physical examination	Advised to continue PT and to follow-up with orthopedic physician, who thought he had rotator cuff syndrome
8/6/18	Continued to have bilateral shoulder, hand, and knee pain. No frank joint swelling. Declined subacromial cortisone injections Rheumatologist believed that elevated ESR and multiple joint pains were suggestive but not diagnostic of inflammatory arthritis. Patient was also having fatigue	Results of radiographs of shoulders were unremarkable Physical examination showed skin mottling on palms	Referred to rheumatologist Advised continued NSAIDs, PT, and activity modification. Also recommended evaluation for OSA
8/10/18	Polysomnogram completed and OSA diagnosed	None	Provided CPAP machine
8/16/18	After 6 wk of body aches, he was now having right-sided chest wall pain and bilateral thigh pain	Creatine kinase level elevated. ANA panel positive for antidouble-stranded DNA and anti-Scl 70	Continued observation
8/20/18	Saw PCP because of cough, diagnosed as postviral	Physical examination	Follow-up as needed
8/22/18	Continued to have bilateral shoulder and thigh pain. Ordered 15-d course of prednisone, 15 mg daily	Physical examination	Patient's pain completely resolved after 3 d, and he stopped taking prednisone
8/29/18	Patient admitted to hospital for treatment of sepsis after 2 wk of cough and 1 day of chest pain. Recent travel to western Canada. Started treatment with ampicillin-sulbactam (Unasyn)	CT angiogram of chest to rule out pulmonary embolism revealed esophagitis/mediastinitis	Continued antibiotics. Infectious disease specialist checked serologic test results for *Coccidioides,* HIV, C3, C4, and aldolase, and urine *Histoplasma* antigen
8/30/18	Patient had normal C3, C4, and aldolase levels. Procalcitonin level was elevated	Physical examination	Continued treatment of presumed bacterial infection
9/7/18	Seen by infectious disease specialist because of low-grade fevers, persistent cough, and red nodular rash on feet. Urine *histoplasma* antigen was positive	Extensive fungal laboratory tests, including testing for *Aspergillus* and *Histoplasma* culture, ordered	Started on short course of itraconazole
9/24/18	Follow-up CT scan of chest consistent with granulomatous mediastinitis	Physical examination	Advised having PET scan to further characterize abnormality
9/28/18	PET scan showed interval decrease in mediastinitis but showed large lymph nodes above and below the diaphragm	Physical examination	Referred to oncologist
10/2/18	Oncologist evaluated patient for lymphadenopathy (thought possibly caused by lymphoma vs histoplasmosis)	Diagnostic bone marrow biopsy performed	Follow-up with PCP
10/15/18	Bone marrow negative for malignancy. Patient was having night sweats with cough. Serum protein electrophoresis showed MGUS. Violaceous macular rash developed on chest and back	Physical examination	Referred to pulmonologist
10/16/18	Pulmonologist evaluated patient. Patient had been receiving hydrochlorothiazide, hydralazine, and losartan for > 10 y	PFT results normal	Continue benzonatate (Tessalon Perles) for relief of cough. Antihistone antibody checked
10/25/18	Antihistone antibody positive. Possibly had drug-induced lupus. Hydrochlorothiazide and hydralazine regimen stopped. If no improvement, he would get long course of histoplasmosis treatment	Physical examination	Follow-up with PCP
11/2/18	For BP control, he was started on clonidine patch and chlorthalidone regimen. Still was having right wrist pain	Physical examination	Follow-up with rheumatologist
12/17/18	Rheumatologist recommended trial of hydroxychloroquine (Plaquenil) and prednisone taper for treatment of drug-induced lupus	Physical examination	Most symptoms resolved with prednisone dose taper. Follow-up with rheumatologist
3/29/19	Came in for follow-up with rheumatologist. Found to test positive for lupus anticoagulant	Repeated ANA panel and antihistone antibody	Antidouble-stranded DNA and anti-Scl 70 still elevated. Antihistone antibody still elevated but lower. Routine rheumatology follow-up advised

ANA = antinuclear antibody; anti-CPP = anticyclic citrullinated peptide; BP = blood pressure; CPAP = continuous positive airway pressure; CT = computed tomography; ESR = erythrocyte sedimentation rate; MGUS = monoclonal gammopathy of uncertain significance; NSAIDs = nonsteroidal anti-inflammatory drugs; OSA = obstructive sleep apnea; PCP = primary care physician; PET = positron emission tomography; PFT = pulmonary function test; PT = physical therapy; RF = rheumatoid factor.

epigenetic silencing of the *MPO* (myeloperoxidase) and *PR3* (proteinase-3)" proteins encoded by the genes and "breakdown of central tolerance by drug metabolites in slow acetylators of hydralazine."[4]

Because DIL is less likely to have extensive internal organ involvement, examination findings such as hepatosplenomegaly, renal problems, or neurologic findings are less common.[6] However, serositis can be seen. Our patient's presentation was a little muddled because the serositis in DIL manifests as pleuritis or pericarditis, with peritonitis being less common. Mediastinitis, as our patient experienced, is unusual. However, granulomatous mediastinitis can be seen in chronic infections such as histoplasmosis or tuberculosis. Therefore, this patient's presentation may have been confounded by *Histoplasma* infection. Typical laboratory findings in DIL include anemia, leukopenia, thrombocytopenia, elevated erythrocyte sedimentation rate, positive ANA, and positive antihistone antibodies.[5]

This case highlights the inherent challenge in diagnosing DIL, as with many rheumatologic conditions that generally require a pattern of signs and symptoms to evolve over time before the diagnosis becomes clear. Sosenko et al[7] noted that DIL diagnosis is further complicated by the fact that although there are "established criteria for the diagnosis of SLE, no formal or universal diagnostic criteria for DIL have been established. The syndrome of DIL results in symptoms" and "laboratory findings consistent with SLE," but "these findings should be related to drug exposure." This topic is important not only for rheumatologists but also for primary care practitioners practicing in the community, because many of the triggers of DIL are commonly prescribed. DIL can be difficult to recognize in clinical practice for a multitude of reasons: "Delayed insidious association between drug exposure and symptom onset, rapid introduction of new drugs developed with limitations in predicting their long-term effect during treatment, and lack of understanding the pathophysiologic mechanisms in DIL."[8] It is interesting that the patient had chest imaging (CT) findings consistent with mediastinitis, when mediastinitis is not typically associated with autoimmune disease.

This case serves as a reminder for physicians in the outpatient clinic that rheumatologic conditions tend to declare themselves over time, as opposed to immediately displaying all the classic clinical manifestations of the disease. It will become ever more important to recognize medication-induced lupus syndromes given the expanding list of medications (some of them very commonly used) associated with DIL. Furthermore, biologics that antagonize tumor necrosis factor (TNF)-α have also been implicated in DIL but are being increasingly used since they were first introduced in 1998 to treat chronic inflammatory conditions such as rheumatoid arthritis and Crohn disease.[1] There is an inherent difficulty in distinguishing true drug-induced autoimmunity from exacerbation of preexisting autoimmunity or unmasking of a second autoimmune disease.[1]

Per Araújo-Fernández et al,[2] TNF-α antagonist-induced lupus syndrome (TAILS) has most commonly been associated with infliximab "because it is the most immunogenic, based on its chimeric structure and its ability to reach high tissue concentrations." Authors of several prospective studies have shown that ANAs develop in patients receiving treatment with anti-TNFα drugs.[2] These lupuslike syndromes develop in approximately 2 per 1000 patients receiving TNFα antagonists.[2] There are several theories why TAILS may occur. Anti-TNFα drugs might induce cell apoptosis, prompting release of antigenic particles as nucleosomes that may lead to formation of autoantibodies.[2] Alternatively, these medications may induce immunosuppression, leading to increased risk of infection and a higher bacterial DNA load that can stimulate polyclonal B-lymphocytes and induce anti-dsDNA antibodies.[2] Last, anti-TNFα medications can suppress the T-helper cell 1 immune response and favor a T-helper 2 response.[2] Araújo-Fernández et al[2] also note, "Although the development of ANAs and anti-dsDNA antibodies is higher in patients receiving anti-TNF treatment, the incidence of TAILS is low, estimated to be between 0.5 and 1.0%." Anti-TNFα-induced DIL shows no important differences compared with the other drugs, so the most common symptoms still include arthritis, myositis, and serositis.[2]

More recently, another mechanism of autoimmunity has been proposed, called NETosis. This is a unique mechanism of neutrophil cell death that has been described in DIL. Per Vaglio et al[3]:

[It is] characterized by the extrusion of a meshwork of intracellular granular proteins bound to chromatin. This process plays a primary role in the host defense against pathogens; however, enhanced formation of neutrophil extracellular traps (NETs) and delayed NET clearance has been associated with various autoimmune diseases. … Peptidylarginine deiminase 4 (PAD4) is a calcium-dependent enzyme that mediates chromatin decondensation in neutrophils, a critical process in NET formation. In fact, hydralazine has been shown to promote NET formation via increasing intracellular calcium flux in vitro, [which activates PAD4 and triggers NET formation].

Even after discontinuation of the offending hydralazine therapy and receiving both corticosteroids and hydroxychloroquine, the patient's anti-dsDNA antibodies remained elevated. In some case studies there were reports of serologic samples remaining positive for up to 1 year. However, in DIL, normally antihistone antibodies are positive (although this is also dependent on the offending drug), but anti-dsDNA antibodies tend to be negative, unlike in SLE. Also, our patient not only had anti-dsDNA antibodies, which is atypical for DIL, but also recently tested positive for lupus anticoagulant. Lupus anticoagulant (a misnomer because it is actually a procoagulant but in the past interfered with coagulation-measuring assays) is one of the antiphospholipid antibodies that can be found even in healthy individuals. However, lupus anticoagulant can be positive in idiopathic SLE or can develop as a result of certain drug exposures. Although ANAs and antihistone antibodies are commonly associated with DIL, antiphospholipid antibodies are relatively rare in hydralazine-induced lupus.[9] Our patient's symptoms were ascribed to hydralazine-induced lupus syndrome, but perhaps the hydralazine served to unmask undiagnosed idiopathic SLE in this patient because the anti-dsDNA antibodies and presence of lupus anticoagulant are atypical in DIL.[10-12] Possibly, once a patient has had a diagnosis of DIL, s/he has demonstrated a

higher propensity for autoimmunity. These patients with DIL may benefit from future monitoring for development of SLE or other autoimmune conditions.

CONCLUSION

Rheumatic diseases are usually evolving and tend to declare themselves with time. Our patient's case highlights how DIL should be on the differential diagnosis when seemingly disparate symptoms develop in a patient receiving DIL-associated medications. The list of medications associated with lupuslike syndromes is growing, including the now popular class of anti-TNFα drugs. Lupus is one of the "great imitators," in which symptoms can be ascribed to many different conditions. Perhaps such a costly workup (in terms of time, cost, and invasive testing) could have been avoided or truncated had DIL been considered earlier. However, in clinical practice many mimickers of the patient's symptoms would need to be ruled out first, making a narrowed diagnostic approach even more challenging.

Although this patient's presentation may have been confounded by concomitant *Histoplasma* infection, his improvement with cessation of hydralazine therapy argues in favor of DIL. This patient's continued atypical serologic test results could be residual from his bout of DIL and should normalize with time. However, it also raises the question whether this episode of DIL has unmasked a previously quiescent autoimmune condition that would require continued observation. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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